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Optimal tigecycline dosage regimen is urgently needed: results from a pharmacokinetic/pharmacodynamic analysis of tigecycline by Monte Carlo simulation

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SUMMARY

Background: The number of reported cases of resistance to tigecycline is increasing. The aim of this study was to evaluate the current standard tigecycline dosage regimen from a pharmacokinetic/pharmacodynamic (PK/PD) perspective.
Methods: Pharmacokinetic parameters and microbiological data were analyzed by Monte Carlo simulation in an evaluation of effectiveness.
Results: Tigecycline exhibits excellent in vitro antimicrobial activity, however the standard tigecycline dosing regimen fails to achieve the best outcome in vivo for the common drug-resistant strains, including *Acinetobacter baumannii*, *Enterobacter spp*, and *Klebsiella pneumoniae*. This may result in a lack of response to tigecycline therapy or to a further increase in the resistance rate.
Conclusions: In the absence of new drugs on the horizon, rather than using a single fixed dosing regimen, tigecycline dosing needs to be optimized in order to achieve the desired successful clinical response and to prevent an escalation in drug resistance.

1. Introduction

Tigecycline, a novel intraven
antibiotic, was approved for the
abdominal infections (cIAI) and complicated skin and skin-structure infections (cSSSI) in 2005 by the US Food and Drug Administration (FDA). This antibiotic has demonstrated an expanded spectrum of in vitro activity and clinical potency against Gram-positive and Gram-negative aerobic and anaerobic bacteria, as well as against antibiotic-resistant strains.[1–4] Tigecycline is also indicated for the treatment of community-acquired bacterial pneumonia.[5] More importantly, Kumarasamy et al.[6] have reported the presence of New Delhi metallo-β-lactamase 1 (NDM-1) among Gram-negative bacteria, and these bacteria are highly resistant to all antibiotics except tigecycline and colistin. Tigecycline has been

ment of difficult-to-treat infections.

However, several failures of tigecycline therapy have occurred in recent years, as has been seen in ventilator-associated bacterial pneumonia (VAP) and other bacterial infections. These failures are likely due to the development of tigecycline resistance and perhaps to inadequate dosing. Since 2007, clinical resistance to tigecycline has been reported in many pathogens, including *Acinetobacter spp*, *Klebsiella spp*, *Enterobacter spp*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Serratia marcescens*, and the prevalence of tigecycline resistance has been found to vary worldwide over the years.[7–18] Thus, the use of the only constant tigecycline dosage regimen against a wide range of bacteria with variable minimum inhibitory concentrations (MIC) may be ineffective and lead to a further increase in antibiotic-resistant strains. (The standard, common dosage regimen for tigecycline for all of these pathogenic organisms is a 100-mg loading dose, followed by 50 mg every12 h for at least 5 days and not more than 14 days.[19])

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Therefore, a pharmacokinetic/pharmacodynamic (PK/PD) evaluation of the magnitude of efficacy of the empirical tigecycline dosage regimen for polymicrobial infections is needed. In a model of murine *Acinetobacter baumannii* pneumonia, tigecycline efficacy was predicted successfully by the relationship between the area under the free concentration–time curve and the MIC (*f*AUC/MIC).[20] In this study, the ratio of the 24-h area under the concentration–time curve and the MIC ($AUC_{(0-24)}$/MIC) was chosen as the PK/PD index for tigecycline, as this index is considered the most likely to be predictive of efficacy.[21]

In the present study, a Monte Carlo simulation was used to calculate the probability of attaining targeted pharmacodynamic exposure against a wide range of isolates with variable MICs from cIAI and cSSSI patients to evaluate the efficacy of the commonly used tigecycline dosage regimen from a PK/PD perspective. Based on this, we also compared different therapeutic schemes of tigecycline to investigate whether the standard dosage regimen achieves the optimal treatment.

2. Methods

The methodology included: (1) acquisition of pharmacokinetic parameters and microbiological information, (2) Monte Carlo simulation, and (3) forming an estimate of the probability of target attainment (PTA, defined as the probability that at least a specific value of a PK/PD index is achieved at a certain MIC) and calculation of the cumulative fraction of response (CFR, defined as the expected population probability of target attainment for a specific drug dose and a specific population of microorganisms).[22,23]

2.1. Pharmacokinetic parameters and microbiological information

The pharmacokinetic parameters of tigecycline were obtained from published studies.[24] The phase 1 studies were randomized, double-blind, single-center, and placebo-controlled. Pharmacokinetic studies were identified using the PubMed NLM search engine for the MEDLINE database. Studies were included if they evaluated clinically relevant dosing regimens and provided the means for the pharmacokinetic parameters of interest with the corresponding variability.

In this work, pathogens in the cSSSI and cIAI patient populations were selected for analysis. Gram-positive pathogens isolated from the infection site of patients with cIAI and cSSSI included *S. aureus*, streptococci, and *Enterococcus spp*, among which *S. aureus* and streptococci were the predominant pathogens for cSSSI.[25] In addition, the isolated pathogenic Gram-negative and anaerobic bacteria included *A. baumannii*, *Citrobacter spp*, *Enterobacter spp*, *Escherichia coli*, *Klebsiella spp*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Shigella dysenteriae*, *S. marcescens*, and *Bacteroides fragilis*. The predominant pathogens for cIAI were *E. coli* and *B. fragilis*.[26] The MIC distributions of the selected Gram-positive and Gram-negative bacteria isolates were those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). According to EUCAST, the tigecycline MICs for these pathogens are mainly distributed between 0.004 and 16 mg/l. Data were obtained from the EUCAST MIC distribution website (http://www.eucast.org, last accessed April 10, 2013). The distributions are based on collated data from a total of more than 24 000 MIC distributions from worldwide sources. The distributions include MICs from national and international studies, including resistance surveillance programs (Alexander, BSAC, ECO-SENS, MYSTIC, NORM, and SENTRY), as well as MIC distributions from published articles, the pharmaceutical industry, veterinary programs, and individual laboratories. EUCAST interpretive breakpoints were used for evaluation of the efficacy of tigecycline.[27]

2.2. Monte Carlo simulation

The pharmacokinetic parameters were defined as the lognormal distribution obtained with a mean and a percentage coefficient of variance (CV%); in the case of the MIC, a discrete distribution ranging from 0.004 to 64 mg/l based on reported data was considered according to statistical criteria. A Monte Carlo

Table 1
Frequency distribution of tigecycline MICs for the selected Gram-positive and Gram-negative and anaerobic pathogens from the EUCAST MIC distribution website

		MIC (mg/l)													Susceptibility breakpoint (mg/l)
	n	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	
Gram-positive pathogens															
Staphylococcus aureus	1363				0.37	33.16	49.60	15.77	0.81	0.22	0.07				≤0.5, EUCAST
MRSA	286						9.09	76.22	14.34	0.35					≤0.5, FDA
Streptococcus agalactiae	308			10.06	18.83	18.18	49.03	3.90							≤0.25, EUCAST
Streptococcus anginosus	244		0.41	1.64	3.28	69.67	21.31	3.28	0.41						N/A
Streptococcus constellatus	97			1.03	3.09	86.60	7.22		2.06						N/A
Streptococcus pyogenes	419			16.23	16.23	52.27	14.32	0.72	0.24						≤0.25, EUCAST
Streptococcus intermedius	26	3.85	3.85		30.77	34.62	15.38	3.85	3.85	3.85					N/A
Enterococcus faecalis	1150			0.26	9.74	44.52	30.96	14.00	0.52						≤0.25, EUCAST
Enterococcus faecium	799			0.63	19.90	55.69	20.53	3.00	0.13	0.13					≤0.25, EUCAST
Gram-negative pathogens															
Escherichia coli	4237					2.08	31.65	46.50	15.55	3.42	0.52	0.19	0.07	0.02	≤1.0, EUCAST
Acinetobacter baumannii	299				0.67	8.03	11.37	17.06	21.07	20.74	17.06	4.01			≤2.0, FDA
Citrobacter freundii	215				2.79	1.40	11.16	46.05	26.05	8.84	2.79		0.93		≤1.0, EUCAST
Citrobacter koseri	203					0.99	18.72	60.59	17.73	1.48	0.49				≤1.0, EUCAST
Enterobacter cloacae	894						0.34	10.96	52.01	26.96	5.70	2.13	1.68	0.22	≤1.0, EUCAST
Klebsiella oxytoca	613						5.22	45.02	41.76	5.55	1.63	0.82			≤1.0, EUCAST
Klebsiella pneumoniae	1856					0.05	0.92	14.87	49.62	23.11	7.76	3.23	0.32	0.11	≤1.0, EUCAST
Proteus mirabilis	1197						0.17	0.33	2.26	17.71	28.74	36.93	13.62	0.25	N/A
Pseudomonas aeruginosa	944						0.11	0.53	0.85	1.69	2.22	12.39	38.98	43.22	N/A
Shigella dysenteriae	159					3.14	35.22	47.17	11.32	2.52	0.63				N/A
Serratia marcescens	257							1.56	21.40	63.81	11.28	1.17	0.78		≤1.0, EUCAST
Anaerobic pathogen															
Bacteroides fragilis	1663			0.18	0.12	6.37	5.05	13.89	19.36	24.53	18.64	4.75	4.03	3.07	≤4.0, FDA

MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*; N/A, not available.

simulation[28,29] with 10 000 subjects was performed using Crystal Ball software (Fusion Edition, version 11.1.1.1.00; Oracle).

The steady-state $AUC_{(0-24)}$ data for tigecycline obtained directly from the selected published study,[24] with the dose regimens of 50 mg and 100 mg every 12 h, were 6.14 ± 12% and 9.96 ± 19% μg.h/ml (mean ± CV%), respectively. An $AUC_{(0-24)}$/MIC >17.9[25] and $AUC_{(0-24)}$/MIC >6.96[26] were the PK/PD targets of tigecycline identified by classification and regression tree (CART) analysis[30] for the treatment of cSSSI and cIAI, respectively. The corresponding PTA was calculated with one fixed MIC value ranging from 0.004 to 64 mg/l, and the calculation of the CFR utilizing the data from the EUCAST MIC distribution, with a CFR result of >90% representing an optimal regimen against a population of organisms.

3. Results

Table 1 shows the frequency of MIC distributions of several significant pathogens from cSSSI and cIAI for tigecycline based on EUCAST data. Differences were investigated for tigecycline susceptibility among the Gram-positive and Gram-negative pathogens.

3.1. MIC distribution of Gram-positive pathogens

For the Gram-positive bacteria, 100% of the total isolates presented MICs ≤2 mg/l for tigecycline, with 99.54% of the isolates exhibiting MICs ≤0.5 mg/l. In total, 4692 Gram-positive bacteria isolates were collected during this study, with 1363 *S. aureus* isolates, 286 methicillin-resistant *S. aureus* (MRSA) isolates, and 1949 *Enterococcus spp* isolates showing a high level of susceptibility to tigecycline (99.71%, 99.65%, and 99.62%, respectively). Similar susceptibility rates of *Streptococcus agalactiae* and *Streptococcus pyogenes* were recorded for tigecycline (100% and 99.76% susceptible, respectively). The susceptibility breakpoints for the other *Streptococcus spp* isolates to tigecycline were not available (Table 1).

3.2. MIC distribution of Gram-negative and anaerobic pathogens

For the Gram-negative and anaerobic bacteria, the corresponding MIC values for *Citrobacter koseri* and *S. dysenteriae* were ≤2 mg/l; for *A. baumannii* and *Klebsiella oxytoca* were ≤4 mg/l; for *Citrobacter freundii* and *S. marcescens* were ≤8 mg/l; and for *E. coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *P. mirabilis*, *P. aeruginosa*, and *B. fragilis* were ≤16 mg/l. A total of 10 874 Gram-negative isolates were collected during this study. High tigecycline susceptibility rates of 99.20%, 97.90%, and 97.55% were found for *E. coli*, *Citrobacter spp*, and *K. oxytoca* strains, respectively. *A. baumannii* and *B. fragilis* had relatively lower susceptibility compared with the aforementioned strains, of 95.99% and 92.9%, respectively. However, significant decreases in tigecycline susceptibility were noted in strains of *E. cloacae* (90.27%), *K. pneumonia* (88.57%), and *S. marcescens* (86.77%). The susceptibility breakpoints of *P. mirabilis*, *P. aeruginosa*, and *S. dysenteriae* isolates to tigecycline were not available (Table 1).

3.3. PTA analysis

Figures 1 and 2 show the probability of PK/PD target attainment by MIC for the antibiotic studied at the selected dosing regimens. On the basis of simulation results, the use of tigecycline 50 mg or 100 mg every 12 h provided a PTA ($AUC_{(0-24)}$/MIC >17.9, for cSSSI) higher than 99% for MICs ≤0.25 mg/l. With the dose regimens of 50 mg and 100 mg every 12 h, respectively, the corresponding PTA values were 0% and 67.98% for a MIC of 0.5 mg/l. The PTA values remained at zero for a MIC higher than 0.5 mg/l (Figure 1).

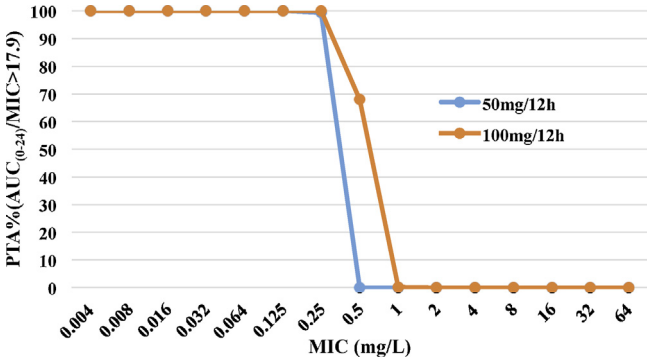

Figure 1. Probability of target attainment as a function of the MIC for 10 000 simulated subjects given tigecycline. The chosen target was $AUC_{(0-24)}$/MIC >17.9 for complicated skin and skin-structure infection (cSSSI) patients.

The selected targets for cIAI were $AUC_{(0-24)}$/MIC >6.96, and the tigecycline dosage regimens of 50 mg and 100 mg every 12 h both provided PTA values of 100% for a MIC ≤0.5 mg/l. Different PTA values were demonstrated between 50 mg and 100 mg every 12 h for a MIC of 1 mg/l, with values of 12.93% and 96.6%, respectively. The PTA values remained at zero for a MIC higher than 2 mg/l (Figure 2).

3.4. CFR analysis

Table 2 shows the assessment of CFR for different tigecycline dosage regimens evaluated based on the $AUC_{(0-24)}$/MIC >17.9 in the treatment of cSSSI and the $AUC_{(0-24)}$/MIC >6.96 in the treatment of cIAI. Regarding Gram-positive bacteria isolated from cSSSI patients, average CFR values of higher than 90% were obtained with the use of the standard dose regimen 50 mg every 12 h (97.50%) and the higher dose of 100 mg every 12 h (99.17%). Whilst the values of CFR for the MRSA isolates (84.81%) and *S. dysenteriae* isolates (85.22%) with the dose of 50 mg every 12 h were lower than 90%, the corresponding CFR values remained higher than 90% when the dose was augmented to 100 mg every 12 h. Significant decreases in CFRs were noted in the Gram-negative bacteria isolates from cSSSI patients, showing a total mean value of 38.44% and 54.67%, with 50 mg and 100 mg every 12 h doses, respectively. Tigecycline was rarely active against *P. mirabilis* strains (CFR varied from 0.5% to 2.05%), *P. aeruginosa* strains (CFR varied from 0.64% to 1.22%), and *S. marcescens* (CFR varied from 1.66% to 16.28%) on the basis of the varied dose regimens.

CFR values obtained with tigecycline ($AUC_{(0-24)}$/MIC >6.96, for cIAI) are shown in Table 2. The average CFR values of Gram-positive

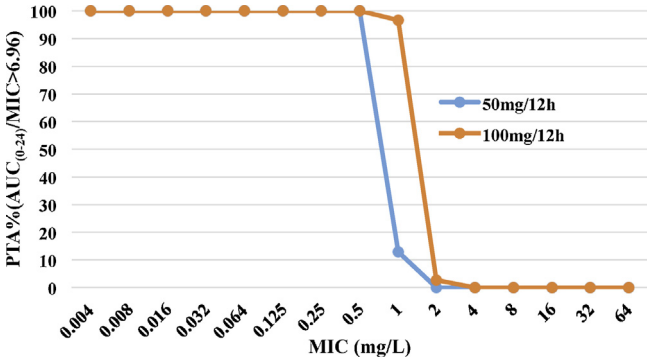

Figure 2. Probability of target attainment as a function of the MIC for 10 000 simulated subjects given tigecycline. The chosen target was $AUC_{(0-24)}$/MIC >6.96 for complicated intra-abdominal infection (cIAI) patients.

Table 2
Expected cumulative fraction of response (CFR) for tigecycline. The chosen targets were $AUC_{(0-24)}$/MIC >17.9 for complicated skin and skin-structure infection (cSSSI) patients and $AUC_{(0-24)}$/MIC >6.96 for complicated intra-abdominal infection (cIAI) patients.[a]

Pathogens	Probability (%) $AUC_{(0-24)}$/MIC >17.9		Probability (%) $AUC_{(0-24)}$/MIC >6.96	
	50 mg q12h	100 mg q12h	50 mg q12h	100 mg q12h
Gram-positive pathogens				
Staphylococcus aureus	98.80	99.45	99.74	99.92
MRSA	84.81	95.06	-	-
Streptococcus agalactiae	99.97	100.0	100.0	100.0
Streptococcus anginosus	99.57	99.87	100.0	100.0
Streptococcus constellatus	97.94	99.34	100.0	100.0
Streptococcus pyogenes	99.77	99.93	-	-
Streptococcus intermedius	-	-	96.67	99.89
Enterococcus faecalis	99.39	99.83	-	-
Enterococcus faecium	99.73	99.84	-	-
Gram-negative pathogens				
Escherichia coli	79.92	90.80	96.22	99.10
Acinetobacter baumannii	37.02	51.47	-	-
Citrobacter freundii	61.10	79.12	88.59	96.07
Citrobacter koseri	79.90	92.35	98.22	99.47
Enterobacter cloacae	11.23	46.68	66.80	89.51
Klebsiella oxytoca	49.94	78.63	92.72	97.41
Klebsiella pneumoniae	15.74	49.59	68.45	88.00
Proteus mirabilis	0.50	2.05	-	-
Pseudomonas aeruginosa	0.64	1.22	-	-
Shigella dysenteriae	85.22	93.23	-	-
Serratia marcescens	1.66	16.28	-	-
Anaerobic pathogens				
Bacteroides fragilis	-	-	48.14	69.18

AUC, area under the curve; MIC, minimum inhibitory concentration; q12 h, every 12 h; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] '-', no corresponding pathogen isolated from the infection site of patients.

bacteria in cIAI were higher than 90% with doses of 50 mg and 100 mg every 12 h. The CFR value of *C. freundii* (88.59%) was only fractionally lower than 90%. Among the remaining isolates, the CFRs of *E. cloacae*, *K. pneumoniae*, and *B. fragilis* were noted to be lower (66.8%, 68.45%, and 48.14%, respectively) with 50 mg every 12 h, and still presented CFRs lower than 90% with the augmented dose of 100 mg every 12 h. CFR values gradually increased with the increase in tigecycline dosing and the reduction in the PD breakpoint (Table 2).

4. Discussion

In the current study, the in vitro activity of tigecycline was assessed against a selection of important Gram-positive and Gram-negative pathogens collected from cSSSI and cIAI patients. Although pathogens isolated from the infection sites of patients were demonstrated to have a varied MIC distribution, they still presented a high level of susceptibility to tigecycline: all wild-type Gram-positive pathogens with available MIC breakpoints had a susceptibility higher than 99%, and for Gram-negative pathogens, this was lower but they were still susceptible to tigecycline. According to Kahlmeter et al.,[27] the tigecycline MIC values for wild-type staphylococci, streptococci, *E. faecalis*, and *Enterococcus faecium* were all ≤0.5 mg/l in 2006. In this study, 99.17% of these Gram-positive isolates exhibited MICs ≤0.5 mg/l, and 0.29% of *S. aureus* pathogens and 0.13% of *E. faecium* pathogens presented MICs ≥1 mg/l; this illustrates the slowly increasing emergence of antimicrobial resistance in these pathogens over the years.

Figures 1 and 2 show that as the tigecycline dose increased, the corresponding theoretical MIC breakpoint, above which the treatment for infection would be ineffective, also improved. For patients with cSSSI, the best treatment outcome was achieved using the standard regimen for all of the Gram-positive pathogens except MRSA, but this failed for all the Gram-negative ones. With the increased dose (100 mg every 12 h) treatment, an optimal dose was obtained for all Gram-positive bacteria including MRSA. The CFR values of Gram-negative bacteria increased markedly, but still the majority were less than 90% with 100 mg every 12 h. In addition, we directly observed that *P. mirabilis*, *P. aeruginosa*, and *S. marcescens* failed to respond to tigecycline; combination therapy may be suggested for such polymicrobial infections as a result of the studies carried out in vitro and in animal models.[31–33] For patients with cIAI, an optimal therapy was achieved against most of the pathogens, however the doses of 50 mg and 100 mg every 12 h both remained poorly active against *B. fragilis*.

With the investigation of tigecycline susceptibility in numerous selected pathogens, tigecycline was found to be one of the most active antimicrobial agents against Gram-positive isolates and also to be effective against Gram-negative ones in vitro, including drug-resistant pathogens. However we also demonstrated that the common drug-resistant strains failed to attain best treatment with the current standard tigecycline dose regimen. This is in concordance with the results of several clinical studies. Consales et al.[34] described an MDR *A. baumannii* (MRAB) outbreak that occurred in the intensive care unit of Prato Hospital in June to August 2009. In that study tigecycline resulted in a rapid recovery, but resistance nevertheless ensued. Similar reports[35–38] have given evidence that tigecycline has a degree of clinical effectiveness in the treatment of complicated infections with MDR strains, however resistance was documented to have occurred in the patients and might have resulted from inappropriate tigecycline dosing. Furthermore, although the efficacy of tigecycline is well-known, we believe that tigecycline is not the best choice in some cases. In the case of VAP, failure of tigecycline is not only related to the enhanced MIC of some MDR bacteria such as *A. baumannii*, but also to a decrease in $AUC_{(0-24)}$.[39] According to Burkhardt et al.,[40] alveolar cell concentrations are high but extracellular epithelial lining fluid concentrations of tigecycline are insufficient to reliably eradicate extracellular bacteria in the case of a mechanically ventilated patient. Therefore, the current dosage of 50 mg

tigecycline twice daily is probably an under-dose for the treatment of pneumonia caused by typical, extracellular-acting bacteria. Meanwhile, it is noted that the higher dose regimen may not be tolerated due to gastrointestinal side effects, which is also an important factor in discussing optimal tigecycline dosing. Tigecycline might not be the best choice for infections that cannot be effectively treated with the standard dose and where a higher dose cannot be tolerated.

To guarantee clinical success with conventional tigecycline therapy, based on the findings and limitations of this study, we can conclude that: (1) With MICs $\leq$0.25 mg/l, the use of standard tigecycline dosing is predicted to have a good clinical outcome at AUC_{0-24}/MIC >17.9 for cSSSI patients, whilst with MICs $\leq$0.5 mg/l, the desired clinical outcome is predicted at AUC_{0-24}/MIC >6.96 for cIAI patients when applying the same dose of tigecycline. In this regard, optimization of the current tigecycline dose use is unavoidable for more effective treatment. (2) Our study revealed the current standard tigecycline dosing regimen to be excellent for Gram-positive infections. The recommendation of tigecycline courses for the treatment of Gram-negative infections with regard to whether tigecycline empirical treatment should be retained or adjusted, should be based on the value of the expected CFR and other factors. (3) Finally, this study reinforces the idea of considering not only the antimicrobial MIC distribution but also the PK/PD index of AUC_{0-24}/MIC ratios to increase the probability of clinical success in the treatment of patients with different infections.

Further work needs to focus on the optimization of tigecycline dose regimens for the treatment of different infections with specific pathogens. Rational drug use is important to prevent an escalation in antimicrobial resistance and to maximize the likelihood of a favorable clinical response, as well as to minimize the probability of exposure-related toxicity.

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Conflict of interest: The authors declare that no competing interests exist.

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